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EXAMINER	
BERTAGNA, ANGELA MARIE	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 01/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/500,831	KARLSEN, FRANK	
	Examiner	Art Unit	
	Angela Bertagna	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,8,9,16,21,22,25-27 and 29-31* is/are pending in the application.

4a) Of the above claim(s) *8,9,16,21,22,25-27, 29, and 31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claims 1-5, 8, 9, 16, 21, 29, and 30, drawn to oligonucleotide primers, primer pairs, primer/probe sets, and a reagent kit for use in the detection of human papillomavirus (HPV) by nucleic acid based sequence amplification.

Group II, claims 22, 25-27, and 31, drawn to methods of detecting HPV mRNA in a test sample.

2. The inventions listed as Groups I and II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Cerutti et al. (US Patent No. 5,750,334) teach the use of polymerase chain reaction for the detection of mRNA transcripts from the HPV E6 gene (see column 2, lines 1-38) and disclose an oligonucleotide comprising the instant SEQ ID No: 1 in Example 4b (columns 5-6). Since Certucci et al. anticipate claim 1, the claims lack a special technical feature over the prior art that links the claimed invention. Therefore, a lack of unity requirement is proper.

3. Further Restriction Requirement Applicable to All Groups:

Additionally, each of Groups I and II named above is subject to a further restriction. Applicant is required to further elect three specific sequences for examination. For example, the applicant may select a primer pair for detection of mRNA transcripts from the E6 gene of HPV and an oligonucleotide probe sequence.

With regard to the election of a single sequence, different nucleotide sequences are structurally distinct chemical compounds and are unrelated to one another. These sequences are thus deemed to normally constitute independent and distinct inventions within the meaning of 35 U.S.C 121. Absent evidence to the contrary, each such nucleotide sequences are presumed to represent an independent and distinct invention, subject to restriction requirement pursuant to 35 U.S.C. 121 and 37 CFR 1.141. By statute, "[i]f two or more independent and distinct inventions are claimed in one application, the Commissioner may require the application to be restricted to one of the inventions." 35 U.S.C. 121. Pursuant to this statute, the rules provide that "[i]f two or more independent and distinct inventions are claimed in a single application, the examiner in his action shall require the applicant...to elect that invention to which his claims shall be restricted." 37 CFR 1.142 (a). See also 37 CFR 1.141(a).

The search and examination of all possible groups would pose an enormous burden on the examiner and on the PTO search resources. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as demonstrated by their different classification and recognized divergent subject matter due to all of the inventions' different gene sequences would require different searches that are not coextensive, examination of these claims would pose a serious burden on the examiner and therefore the restriction is deemed proper.

4. The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is

subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of In re Ochiai, In re Brouwer and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.** Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply

where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

5. During a telephone conversation with John Van Amsterdam on November 14, 2005 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-5, 8, 9, 16, 21, 29, and 30. In addition, with regard to the further requirement for restriction, a provisional election was made with traverse to prosecute the invention of Group I with respect to SEQ ID Nos: 16, 18 and 20. Affirmation of this election must be made by applicant in replying to this Office action. Claims 8, 9, 16, 21, 22, 25-27, 29, and 31 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Note that although claims 8, 9, 16, 21, and 29 have been placed in Group I, the election of SEQ ID Nos: 16, 18 and 20 results in these claims being drawn to a non-elected invention. Therefore, claims 8, 9, 16, 21 and 29 have been withdrawn from further consideration.

Claim Rejections - 35 USC § 101

7. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

8. Claims 1-5 and 30 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Specifically, the claims are directed to products of nature. Insertion of the phrase "isolated and purified" before the

word "oligonucleotide" and after the word "An" in claim 1 would direct the claimed invention toward statutory subject matter.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

11. Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Von Knebel-Doberitz et al. (US Patent No. 6,027,891). Note that the restriction requirement made above limits the claims to the elected sequences, SEQ ID Nos: 16, 18 and 20.

With regard to claim 1, Knebel-Doberitz et al. disclose an oligonucleotide molecule for use in the detection of mRNA transcribed from the E6 gene of a human papillomavirus, the oligonucleotide comprising any one of sequence numbers 1-133. SEQ ID Nos: 4 and 22 of Knebel-Doberitz et al. are oligonucleotide primers of 21 nucleotides that contain the exact complement of the instant SEQ ID No: 20 with the addition of a single thymine nucleotide at the 5' end (see sequence listing). Knebel-Doberitz et al. further disclose that SEQ ID No: 4 is a suitable primer for the E6-E7 region of HPV (column 2, line 65 – column 3, line 15). This disclosure by Knebel-Doberitz et al. meets the limitations of the instant claim.

With regard to claim 2, Knebel-Doberitz et al. disclose an oligonucleotide molecule according to the instant claim 1 which is an oligonucleotide primer selected from: a NASBA P1 primer comprising sequence number 20, a NASBA P2 primer comprising sequence number 16, and a PCR primer comprising sequence number 16. As discussed above, SEQ ID Nos: 4 and 22 of Knebel-Doberitz et al. contain the exact complement of the instant SEQ ID No: 20 with the addition of a single thymine nucleotide at the 5' end (see sequence listing), thereby meeting the limitations of the instant claim.

11. Claims 1 and 2 are rejected under 35 U.S.C. 102(e) as being anticipated by Anthony et al. (US Pub No. 2004/0214302 A1). This application derives priority from Application No. 09/594,839 filed on June 15, 2000. Also, note that the restriction requirement made above limits the claims to the elected sequences, SEQ ID Nos: 16, 18 and 20.

With regard to claim 1, Anthony et al. disclose an oligonucleotide molecule for use in the detection of mRNA transcribed from the E6 gene of a human papillomavirus, the oligonucleotide comprising any one of sequence numbers 1-133. SEQ ID No: 95 of Anthony et al. is an oligonucleotide of 33 nucleotides that contains the exact sequence of the instant SEQ ID No. 20 with an additional seven nucleotides at the 5' end and an additional six nucleotides at the 3' end (see sequence listing, page 35), thereby meeting the limitations of the instant claim.

With regard to claim 2, Anthony et al. disclose an oligonucleotide molecule according to the instant claim 1 which is an oligonucleotide primer selected from: a NASBA P1 primer comprising sequence number 20, a NASBA P2 primer comprising sequence number 16, and a PCR primer comprising sequence number 16. As discussed above, SEQ ID No: 95 of Anthony et al. contains the exact sequence of the instant SEQ ID No. 20 with an additional seven nucleotides at the 5' end and an additional six nucleotides at the 3' end (see sequence listing, page 35), thereby meeting the limitations of the instant claim.

12. Claims 1 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Cummins et al. (US Patent No. 5,654,416). Note that the restriction requirement made above limits the claims to the elected sequences, SEQ ID Nos: 16, 18 and 20.

With regard to claim 1, Cummins et al. disclose an oligonucleotide molecule for use in the detection of mRNA transcribed from the E6 gene of a human papillomavirus, the oligonucleotide comprising any one of sequence numbers 1-133. SEQ ID No: 36 of Cummins et al. is an oligonucleotide of 28 nucleotides that contains the exact sequence of the instant SEQ ID No: 18 with an additional five nucleotides at the 5' end and two additional nucleotides at the 3' end (see sequence listing, column 43). This disclosure meets the limitations of the instant claim.

With regard to claim 5, Cummins et al. disclose an oligonucleotide molecule according to claim 1 which is a probe for use in the detection of mRNA transcribed from the E6 gene of a human papillomavirus comprising sequence number 18. As discussed

above, Cummins et al. disclose in SEQ ID No: 36 an oligonucleotide of 28 nucleotides that contains the exact sequence of the instant SEQ ID No: 18 with an additional five nucleotides at the 5' end and two additional nucleotides at the 3' end (see sequence listing column 43). As discussed above, Hendricks et al. disclose a 38 bp oligonucleotide probe for detection of HPV that contains the exact complement of the sequence of the instant SEQ ID No. 18 with an additional seventeen nucleotides at the 5' end (Figure 3, probe no. 18-4). This disclosure meets the limitations of the instant claim.

13. Claims 1 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Hendricks et al. (WO 91/08312). Note that the restriction requirement made above limits the claims to the elected sequences, SEQ ID Nos: 16, 18 and 20.

With regard to claim 1, Hendricks et al. disclose an oligonucleotide probe of 38 nucleotides for detection of HPV that contains the exact complement of the instant SEQ ID No. 18 with an additional seventeen nucleotides at the 5' end (Figure 3, probe no. 18-4). This disclosure meets the limitations of the instant claim.

With regard to claim 5, Hendricks et al. disclose an oligonucleotide molecule according to claim 1 which is a probe for use in the detection of mRNA transcribed from the E6 gene of a human papillomavirus comprising sequence number 18. As discussed above, Hendricks et al. disclose a 38 bp oligonucleotide probe for detection of HPV that contains the exact complement of the sequence of the instant SEQ ID No. 18 with an

additional seventeen nucleotides at the 5' end (Figure 3, probe no. 18-4). This disclosure meets the limitations of the instant claim.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. Claims 1, 2, and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable ~~in view of~~ over Shimada et al. (EP 0 402 132 A2) in view of Buck et al. (Biotechniques, 1999). Note that the restriction requirement made above limits the claims to the elected sequences, SEQ ID Nos: 16, 18 and 20.

With regard to claim 1, Shimada et al. teach an oligonucleotide of 20 nucleotides that matches exactly the sequence of the instant SEQ ID No: 16 (see Table 2, sequence p18-3). The only difference between the instant SEQ ID No: 16 and the oligonucleotide of Shimada et al. is the addition of two nucleotides to the 3' end in the instantly claimed oligonucleotide not present in the oligonucleotide of Shimada et al. In addition, Shimada et al. disclose an oligonucleotide of 20 nucleotides that matches exactly the instantly claimed SEQ ID No: 18 in 18 out of a possible 20 nucleotides (see Table 3, sequence p818 II). The oligonucleotide of Shimada et al. contains two

additional nucleotides at the 5' end (namely, CC) and lacks three nucleotides at the 3' end (namely, ATG) present in the instantly claimed SEQ ID No: 18.

With regard to claim 2, Shimada et al. teach an oligonucleotide of 20 nucleotides that matches exactly the sequence of the instant SEQ ID No: 16 (see Table 2, sequence p18-3). The only difference between the instant SEQ ID No: 16 and the oligonucleotide of Shimada et al. is the addition of two nucleotides to the 3' end in the instantly claimed oligonucleotide not present in the oligonucleotide of Shimada et al.

With regard to claim 5, Shimada et al. disclose an oligonucleotide of 20 nucleotides that overlaps with the instantly claimed SEQ ID No: 18 in 18 out of a possible 20 nucleotides (see Table 3, sequence p818 II). The oligonucleotide of Shimada et al. contains two additional nucleotides at the 5' end (namely, CC) and lacks three nucleotides at the 3' end (namely, ATG) present in the instantly claimed SEQ ID No: 18.

Buck et al. analyzed the effect of primer design strategy on the performance of DNA sequencing primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that every single primer worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, every single control primer functioned as

well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to modify the termini of the oligonucleotides disclosed by Shimada et al. in order to obtain the instantly claimed oligonucletides of SEQ ID Nos: 16 and 18. As noted above, the differences between the instantly claimed oligonucleotides and the oligonucleotides of Shimada et al. are minor - 2-3 nucleotides at the termini are added to the termini of the oligonucleotides of Shimada et al. Absent any disclosed advantage for using the instantly claimed oligonucleotides, the differences appear to stem from user preference rather than an improvement over the oligonucletides of Shimada et al. Furthermore, since Buck et al. clearly demonstrate the equivalence of primer sequences, the ordinary biochemist could have anticipated a reasonable level of success in using the modified primers to amplify mRNA transcripts from HPV.

Attention is also directed to the court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995) where the Court of Appeals for the Federal Circuit determined that the

existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similiarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties". (see page 5 of the attached ref)

As noted above, the prior art of Shimada et al. teaches oligonucleotides comprising the instantly claimed SEQ ID Nos: 16 and 18 with the only differences relating to the addition or subtraction of nucleotides at the termini. Furthermore, Shimada et al. disclose regions of approximately 100 nucleotides designated as useful for primer design for the detection of HPV (Table 1, Sequence 5 (HPV18 from Region II)). Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art of Shimada et al. as useful for primers and probes for the detection of HPV, and in particular for detection of transcripts of the E6 gene, and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited references in the absence of secondary considerations.

16. Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Von Knebel-Dobritz et al. in view of Kievits et al. (Journal of Virological Methods, 1991) and further in view of Yates et al. (Journal of Clinical Microbiology, October 2001).

Von Knebel-Dobritz et al. teach the oligonucleotide primer of claim 2, as discussed above. Specifically, Von Knebel-Dobritz et al. teach an oligonucleotide comprising the instant SEQ ID No: 20.

With regard to claim 3, the oligonucleotide taught by Van Knebel-Dobritz et al. does not have the sequence AATTCTAAATACGACTCACTATAGGGAGAAGG-SEQ where SEQ represents the instant SEQ ID No: 20.

Kievits et al. teach nucleic acid sequence based amplification (NASBA) as a method for detection of HIV-1 in clinical samples (see abstract). In a review of the principles of the method, Kievits et al. note the requirement of an RNA polymerase promoter sequence, such as the sequence for the T7 RNA polymease (AATTCTAATACGACTCACTATAGGG) (see Figures 1 and 2) in order to synthesize the amplified RNA produced by the method.

Yates et al. teach a method for detecting HPV using NASBA and molecular beacon detection. This method uses a P1 NASBA primer containing the sequence AATTCTAAATACGACTCACTATAGGGAGAAGG at the 5' end to function as a T7 RNA polymerase promoter sequence (see Table 1, page 3657).

It would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to modify the oligonucleotide of Von Knebel-Dobritz et al. to contain a T7 RNA polymerase promoter sequence such as AATTCTAAATACGACTCACTATAGGGAGAAGG for use in a NASBA reaction, because Kievits et al. taught that inclusion of such a promoter sequence is essential for conducting the NASBA reaction (see Figures 1 & 2; page 276). Although Kievits et al.

taught the use of a promoter sequence that is 6 nucleotides shorter than the instantly claimed sequence, Yates et al. successfully used a NASBA P1 primer containing the longer, instantly claimed sequence, thereby providing the ordinary artisan with an alternative promoter sequence and a reasonable expectation of success in performing NASBA using such a primer. Moreover, Kievits also taught that NASBA has several advantages over the conventional amplification methods taught by Von Knebel-Dobritz, including being more suitable for amplification of RNA target sequences and lacking the need for thermocycling (page 274). Therefore, one of ordinary skill in the art, interested in obtaining a better amplification of mRNA transcripts from the E6 gene of HPV would have been motivated to modify the oligonucleotide of Von Knebel-Dobritz et al. for use in a NASBA reaction by including a T7 RNA polymerase promoter sequence as taught by Kievits et al., thus resulting in the instantly claimed invention.

17. Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable in view of Shimada et al. (EP 0 402 132 A2) in view of Simpkins et al. (Letters in Applied Microbiology, January 2000). Note that the restriction requirement made above limits the claims to the elected sequences, SEQ ID Nos: 16, 18 and 20.

Shimada et al. teach an oligonucleotide of 20 nucleotides that matches exactly the sequence of the instant SEQ ID No: 16 (see Table 2, sequence p18-3). The only difference between the instant SEQ ID No: 16 and the oligonucleotide of Shimada et al. is the addition of two nucleotides to the 3' end in the instantly claimed oligonucleotide not present in the oligonucleotide of Shimada et al.

Shimada et al. do not teach the use of the oligonucleotide in a NASBA reaction, nor do Shimada et al. teach that the oligonucleotide contain the sequence GATGCAAGGTCGCATATGAG at the 5' end preceding the HPV-specific sequence.

Simpkins et al. teach NASBA for the detection of Salmonella enterica using a NASBA P2 primer containing the sequence GATGCAAGGTCGCATATGAG at the 5' end, where the sequence GATGCAAGGTCGCATATGAG is specific for the Nuclisens™ ruthenium-linked oligonucleotide detection probe (see Primers & probes section, page 76).

It would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to modify the oligonucleotide of Shimada et al. to include the sequence GATGCAAGGTCGCATATGAG for use in the NASBA reaction, because Simpkins et al. taught that inclusion of a generic probe sequence in the NASBA P2 primer is useful for detection of the amplified products using electrochemiluminescence (ECL). Moreover, Simpkins et al. taught that NASBA is more useful for amplification of RNA than the PCR amplification method taught by Shimada et al. One of ordinary skill would have expected the oligonucleotide of Shimada et al. to work reasonably well in a NASBA reaction, because Shimada et al. demonstrated that the oligonucleotide was capable of amplifying HPV, and incorporation of the generic probe sequence GATGCAAGGTCGCATATGAG could have been accomplished using standard synthesis methods known in the art. Therefore, the ordinary artisan, interested in a more efficient RNA amplification method for detection of mRNA transcripts from HPV, would have been motivated to modify the oligonucleotide of Shimada et al. for use in a

NASBA reaction, specifically by incorporating the generic probe sequence GATGCAAGGTCGCATATGAG, in order to detect the NASBA products using ECL, thus achieving the instantly claimed invention.

18. Claim 30 is rejected under 35 U.S.C. 103(a) as being unpatentable over either Cummins et al. or Hendricks et al. in view of Leone et al. (Nucleic Acids Research, 1998) and further in view of either Kievits et al. (J. of Virological Methods, 1991) or Yates et al. (J. of Clinical Microbiology, October 2001).

Cummins et al. and Hendricks et al. disclose an oligonucleotide comprising the oliogonucleotide of claim 5 as discussed above.

With regard to claim 30, Cummins et al. and Hendricks et al. do not disclose that the oligonucleotide is a molecular beacon probe.

Leone et al. teach the use of molecular beacon probes combined with nucleic acid based sequence amplification (NASBA) for detection of RNA of potato leafroll virus (see abstract).

Kievits et al. teach a method of NASBA for the diagnosis of HIV-1 infection (see abstract).

Yates et al. teach a method for the quantitative detection of hepatitis B virus DNA involving NASBA and molecular beacon probes (see abstract).

It would have been prima facie obvious for one of ordinary skill in the art at the time the instant invention was made to apply the method of Leone et al. to the detection of HPV using the oligonucleotide of Cummins et al. or Hendricks et al., because Leone

et al. taught that using molecular beacons to detect NASBA amplicons is an easy method to perform and can be completed more quickly than conventional RNA probing and/or blotting methods without a loss of specificity or sensitivity. Also, the entire reaction can be performed in one tube, minimizing the opportunities for sample contamination (see page 2155, last paragraph). Cummins et al. and Hendricks et al. demonstrated the specificity of the oligonucleotide of the instantly claimed invention in the detection of HPV, and modification of oligonucleotides for use as molecular beacon probes was well known in the art. Therefore, the ordinary artisan would have been expected to have a reasonable expectation of success in modifying the oligonucleotide of Cummings et al. or Hendricks et al. and using it in the method of Leone et al. In addition, the use of NASBA to detect HIV-1 in clinical samples (Kievits et al.) and to quantitatively detect (using molecular beacon probes) hepatitis B virus (Yates et al.) would have further motivated the ordinary artisan to apply this method of NASBA detection using molecular beacons to the detection of HPV using the oligonucleotide of Cummins et al. or Hendricks et al. Thus, a person of ordinary skill in the art, seeking a fast, sensitive and specific method for detecting HPV in real-time, would have been motivated to use the oligonucleotide of Cummings et al. or Hendricks et al. in the method of Leone et al, thus resulting in the instantly claimed invention.

Conclusion

19. No claims are currently allowable over the prior art.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Angela Bertagna whose telephone number is (571) 272-8291. The examiner can normally be reached on M-F 7:00 - 4 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Angela Bertagna
Patent Examiner
Art Unit 1637

amb

JEFFREY FREDMAN
PRIMARY EXAMINER
10/12/11